CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

FENSULFOTHION (DASANIT)
SB 950-153, Tolerance # 234
March 28, 1986
(Revised) March 31, 1987
(Revised) May 5, 1988

I. DATA GAP STATUS

Chronic rat: Data gap. No study on file.

Chronic dog: No data gap. No adverse effect.

Onco rat: Data gap. No study on file.

Onco mouse: Data gap. No study on file.

Repro mouse: Data gap. Inadequate study, no adverse effect indicated.

Terato rat: No data gap. No adverse effect.

Terato rabbit: Data gap. Inadequate studies, possible adverse effect indicated.

Gene mutation: No data gap. No adverse effect.

Chromosome: No data gap. No adverse effect.

DNA damage: Data gap. Inadequate studies, no adverse effect indicated.

Neurotox: No data gap. No adverse effect.

Note: Toxicology one-liners are attached
**** before study number indicates acceptable study**
Boldface study number indicates adverse effect

File name: SB153.JR1 prepared by J. Remsen, 3/28/86; update SB153FEN.JR2 by M. Harnois, 3/28/87; update T880504 by M. Silva, 5/88.

CHRONIC, RAT

No study on file.

CHRONIC, DOG

** 087 59840 "Chronic Feeding Study of Fensulfothion (DASANIT) with Dogs," (Mobay Corporate Toxicology Department, Study No. 85-274-01, Toxicology Report No. 886, stamped No. 94639, 6/30/87). Technical fensulfothion, 92%, was administered in the diet for 1 year at 0 (vehicle = corn oil), 0.5, 1.0, 2.0, or 4.0 ppm to beagle dogs (4/sex/group). ChE NOEL = 1 ppm, Systemic NOEL ≥ 4 ppm. **No adverse effects.** Plasma and erythrocyte cholinesterase activity were significantly inhibited in both males and females at 2.0 and 4.0 ppm. Brain cholinesterase activity was markedly inhibited in both sexes at 4.0 ppm. **Acceptable**. Shimer, 12/16/87. M. Silva, 5/4/88.

234-082 "The Stability of Fensulfothion (DASANIT) in Dog Rations," (Mobay Corporation Environmental Health Research, Corporate Toxicology Department, Toxicology Report# 761, 6/27/86). These data were provided in support of the pilot for study 59840. M. Silva, 5/4/88.

034 922168 "Chronic Oral Toxicity of Bayer 25141 (Dasanit) To Dogs." (U. of Chicago, 1966) Beagle dogs (2 per sex per dose) were fed 1, 2, and 5 ppm for 2 years. Review JW 5/6/85 **Unacceptable**. Inadequate number of animals per group, no dose analysis, no individual data. Also cited as **positive adverse effects** the cholinesterase inhibition noted in the evaluation of the study. Reevaluation (JR and JP, 5/86) indicates the lower cholinesterase activity cited to be **not significant** with respect to chronic adverse effect. Cholinergic symptoms observed in high dose group during the first few weeks of exposure but cleared. NOEL: 2 ppm (clinical signs, change in cholinesterase level). Females more responsive than males.
EPA one-liner: Invalid

ONCOGENICITY, RAT

No study on file

ONCOGENICITY, MOUSE

No study on file

REPRODUCTION, RODENT (mouse)

234-034 922195 "Effect of BAY 25141 in the diet on the reproduction and lactation of mice." (U. of Chicago, 1967.) CF1 mice given 1,2,4,5 and 20 ppm in the diet. Observations on F0, F1, F2, F3b. F3b examined after birth for gross and microscopic changes. Review JW 5/6/85 **Unacceptable** -excessive mortality 20 and 5 ppm with females responding to a greater extent, too few animals per group (6 males, 24 females), inadequate pre-dosing period before mating. **Positive** chronic toxicity with mortality and severe diarrhea but some effects may be due to infection. NOEL: 4 ppm.
Reevaluation by JR and JP, 3/5/86, indicates the study is **unacceptable** but that the results more likely reflect acute toxicity and poor dose selection (complicated by infection or inflammatory processes in some animals) rather than an effect from chronic exposure. The second review decision was that study is **unacceptable** but **no evidence of an adverse effect on reproduction or a chronic effect** indicated in this report.
EPA one-liner: Supplementary. 2 reviews and NOEL's (1 ppm and 4 ppm).

TERATOLOGY, RAT

** 234-071 33963 "A teratology study in the rat with Dasanit." (Miles, 1985.) 28 females/group gavage-dosed with 0.1, 0.25, 0.6 mg/kg on Days 6-15 of gestation. **Acceptable** Maternal toxicity at 0.25 mg/kg. NOEL: 0.6 mg/kg (teratology). AA 9/9/85.
EPA one-liner: Not done

TERATOLOGY, RABBIT

234-048 922193 "Study of embryotoxic and teratogenic effects on rabbits after oral administration." (Bayer, 1978.) 12-13 Himalayan rabbits/group were given 0.1, 0.3, or 1.0 mg/kg by oral gavage, days 6-18 (copulation = Day 0). No overt toxicity. **Unacceptable** (no toxicity in high dose), requested additional data from range-finding study. JW 5/6/85.
EPA one-liner: Supplementary. Awaiting individual data.

234-012 922194 "Teratogenic study with Dasanit technical in Albino rabbits." (Industrial BIO-TEST, 1971.) **Unacceptable** Not validated. JW 5/6/85
EPA one-liner: Invalid

234-084 54352 "A teratology study in the rabbit with Dasanit." (Miles, 2/9/87.) Dasanit technical, 92% AI, in 0.02% aqueous ethanol by oral gavage (3.75 ml/kg) at 0.75, 0.275, 0.1 or 0 mg/kg/day to 17/level American Dutch Belted on gestation days 7-19 (artif. insem. on day 0) with sacrifice on day 28. (Pilot showed 1.25 killed all). No maternal toxicity; day 20 and 28 plasma and rbc (but not day 28 brain) showed AChe inhibition with 0.75 mg/kg; fontanelle enlargement and incomplete skull ossification in all Dasanit groups but no dose response; runting, ectrodactyly, microphthalmia, hermaphroditism; adrenal, spleen, and brain differences in 2 higher groups. **Possible adverse effect.** Maternal NOEL = 0.75 mg/kg/day, tentative developmental NOEL = 0.1. **Unacceptable** but upgradable with historical control data on reported malformations and variations. MH 3/16/87.
EPA one-liner: Not done

MUTAGENICITY, GENE MUTATION

Bacteria

234-076 37330 "Salmonella/microsome test to evaluate for potential point mutation." (Bayer, 1980) TA1535, TA1538, TA98, TA100 $\pm$ S9 (induced rat liver); at 6 levels (0-12500

ug/plate). **Unacceptable** -- no repeat trial, no individual plate counts. **No** increased reversion rate. JR 3/4/86.
EPA one-liner: Not done

234-081 050383 "In vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides - Reverse Mutation in S. typhimurium and E. coli." (SRI, 10/79) Reverse mutation in Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98, and TA100 and in Escherichia coli WP2 uvrA. Tested ± S9 from induced rat liver at 6 levels (1-5000 mcg/plate). Repeat trial. **Unacceptable**--l/group, missing positive control for -S9 set. **No increased reversion rate** but slight toxicity in TA100. MH 3/6/87.
EPA one-liner: Acceptable; negative ± S9.

Conclusion: Although each of the above studies was found unacceptable due to flaws in the design or in the reporting of data, CDFA believes collectively they provide sufficient data to determine whether there is a potential adverse effect.

Mammalian cells

234-070 30913 "CHO/HGPRT mutation assay in the presence and absence of exogenous metabolic activation- Dasanit." (Microbiol. Assoc., 1984.) CHO cultures. 31,63,125,150 nl/ml (-S9) or 100 nl/ml (+S9 from induced rat liver). **Unacceptable** - no repeat trial, contamination with loss of data. **No adverse effect** reported but insufficient information to evaluate. JR 9/6/85.
EPA one-liner: Not done

MUTAGENICITY, CHROMOSOMES

234-012 23501 "Mutagenic study with Dasanit in albino mice (dominant lethal mutations)." (Industrial BIO-TEST, 6/71.) **Unacceptable** --non-validated.
EPA one-liner: Invalid

234-050 922197 "Dominant lethal study on male mice to test for mutagenic effects." (Bayer, 1981.) 50 male NMRI mice were given 1 oral gavage dose of 2 mg/kg in 0.5% Cremophor emulsion at 10 ml/kg; mated 1:1 over 12 periods of 4 days each. **Unacceptable** - single dose, no concurrent positive control; range-finding in females at 1, 2 and 4 mg/kg but males were dosed in the study. **No** adverse effect reported but insufficient information. JW 5/6/85.
EPA one-liner: Not done

234-077 36469 Summary of 234-050 922197.

234-066 27074 "Micronucleus test on the mouse to evaluate for mutagenic effect." (Bayer, 1984.) Fensulfothion (92% AI) was administered in 0.5% Cremophor emulsion orally by gavage 1x to 5 male and 5 female NMRI mice /dose group at 1.5 mg/kg . Dose on basis of pilot study (2.5 mg/kg killed 4/5 but 1.25 mg/kg was NOEL). Cyclophosphamide and vehicle control groups sacrificed at 24 hrs.; test substance animals killed at 24, 48 and 72 hrs. **Acceptable. **No** adverse effect. JR 9/6/85
EPA one-liner: Not done

MUTAGENICITY, DNA/Other

Yeast mitotic recombination

234-081 050703 In vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides - Mitotic Recombination in Saccharomyces cerevisiae." (SRI, 10/79) Dasanit (technical) in DMSO tested at 5 levels (1-50 mg/ml) in 2 trials $\pm$ S9 from induced rat liver. **Unacceptable** --missing positive controls. **No increase in recombinants** MH 3/9/87.
EPA one-liner: Acceptable, negative

Bacterial DNA repair

234-081 050704 "In vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides-DNA Repair in E. coli and B. subtilis." (SRI, 10/79) E. coli (strains W3110 and p3478) and Bacillus subtilis (strains H17 and M45) were used. Dasanit (technical) in DMSO tested at 0.01, 0.1, 1.0, and 5.0 mg/disk without activation system in each of the 4 strains. Positive controls valid. **Unacceptable**--no data with metabolic activation, no indication of diffusion through agar. **No growth inhibition in any strain**. MH 3/10/87.
EPA one-liner: Invalid

Mammalian cell DNA repair

234-081 050705 "In Vitro Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides - Unscheduled DNA Synthesis in Human Fibroblasts," (SRI International, 10/79). Dasanit (technical) in DMSO added to cultures of WI-38 human fibroblast cells at 5 levels in 2 trials at concentrations from 0.1 ug/ml to 1000 ug/ml -S9 and +S9 from uninduced mouse liver. **Unacceptable.** No justification for choice of S9 source. MH 3/11/87. Upon re-evaluation the study status remains **unacceptable** and additional information is required (elaboration of method for conversion of cpm to dpm/ug DNA, elaboration of DNA extraction method, passage number of WI-38 cells, amount of DNA or number of cells/assay, clarification of whether S9 was used in the negative control for the assays with activation). No increase in unscheduled DNA systhesis was observed. **Upgradeable.** M. Silva, 2/25/88.

EPA one-liner: Acceptable, negative

NEUROTOXICITY - HENS

234-034 922164 "Neurotoxic examinations with BAY 25141." (Bayer, 2/65.)
Summary. Hens were dosed at 0.005, 0.01, 0.025, or 0.5 g/kg orally and 0.005, 0.01, 0.025, or 0.05 g/kg by ip injection. **Unacceptable** --insufficient data, no histopathology data.

Deaths >0.01 , no deaths with 0.005 g/kg orally and intraperitoneally; no neurotoxic damage reported.
JW 5/6/85
EPA one-liner: Supplementary. No symptoms or death ≤20 ppm.

**234-068 29588 "Acute delayed neurotoxicity of technical Dasanit in hens." (Mobay, 5/85.) Technical Dasanit (92%), 1.2 g/ml, at 2 mg/kg (pilot median lethal dose) given by oral gavage to 15 White Leghorns (atropine-protected). Repeated in survivors at 21 days. Individual body weights and terminal sacrifice histopath data, summary on clinical and neuromotor findings by individual for weeks 0 and 3 and for by group for weeks 1, 2, 4, 5, 6. Found 5 deaths in Week 0, 1 in Week 3.
Review by AA, 9/6/85 **Unacceptable** --no climbing test Week 3, higher dose level required,indicated **slight reduction in climbing performance Week 2 on**.
Review my MH and GP 3/24/87 **Acceptable**--Week 3 was week that second dose was administered, acute symptoms documented individually; dose is approximate LD and 1st dose killed 5, second dose killed 1. No change in climbing ability Week 2-6. **No acute delayed effect** indicated.
EPA one-liner: Not done